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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,722	10/06/2003	Duane D. Miller	20609/203 (PD 00034)	2869

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EXAMINER	
AULAKH, CHARANJIT	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/679,722	MILLER ET AL.	
	Examiner	Art Unit	
	Charanjit S. Aulakh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-44 are pending in the application.

Claim Rejections - 35 USC § 112

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following eight different factors (see Ex parte Foreman, 230 USPQ at 547; Wands, In re, 858.F. 2d 731, 8 USPQ 2d 1400, Fed. Cir. 1988) must be considered in order for the specification to be enabling for what is being claimed:

Quantity of experimentation necessary, the amount of direction or guidance provided, presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability and the breadth of claims. In the instant case, the specification is not enabling based on atleast four of the above mentioned eight factors such as quantity of experimentation necessary, the amount of direction or guidance provided, presence of working examples, the state of the prior art and the breadth of claims.

The instant specification teaches that there are at least three types of known alpha-2 receptors, namely alpha-2a, alpha-2b and alpha-2c and furthermore, these three subtypes have presumably different localization (presynaptic versus postsynaptic) as

well as different function. The specification further teaches that the instant compounds of formula (I) exhibit binding selectivity for human alpha-2a and alpha-2c receptors over human alpha-2b receptors in vitro experiments. However, the binding affinity data does not demonstrate whether these compounds are agonists or antagonists for alpha-2a and alpha-2c receptors. It is well known in the art that the utility of a compound will be different based on its agonist versus antagonist activity for any receptor type. The demonstration of blockade of medetomidine effects by the instant compounds (again in vitro experiment) and known alpha-2 receptor antagonist, yohimbine suggests that these compounds may act as an antagonists (see data in table 4). However, it is of note that the two compounds tested were found to be 20 to 100 times less potent than yohimbine for alpha-2a receptor and 5 to 35 times less potent for alpha-2c receptors. There is no teaching either in the specification or prior art reference showing any disease condition which is solely mediated by either an agonist activity or an antagonist activity at specific alpha-2 receptor subtype. There are no working examples present showing efficacy of instant compounds in known animal models of any disease condition. The instant compounds of formula (I) encompasses hundreds of thousands of compounds based on the value of linker molecule R and therefore, in absence of such teachings, guidance and presence of working examples, it would require undue experimentation to demonstrate the efficacy of instant compounds in known animal models of every possible disease condition involving etiology of alpha-2a, alpha-2b and alpha-2c receptors and hence their utility for treating but not preventing these disease conditions.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In independent claims 1, it is not clear whether the condition or disorder is mediated by either an agonistic activity at specific alpha-2 receptor subtype or an antagonistic activity at specific alpha-2 receptor subtype and furthermore, these conditions or disorders related to specific alpha-2 receptor subtypes are not defined. Also, the term ---preventing---is indefinite since the degree of prevention (20%, 40%, 60%, 80% or 100%) is not defined. Yohimbine is well known in the art to have alpha-2 receptor antagonist activity and therefore, it is not clear how the linker R in the instant compounds of formula (I) affords activity as an alpha-2 receptor antagonist.

Claim 4 recites the limitation "compound" in claim 2. There is insufficient antecedent basis for this limitation in the claim.

In independent claims 24 and 34, the term ---modulating---is indefinite since it is not clear whether the activity is partially or fully agonized versus antagonized and furthermore, where the activity is being modulated ? Is it in vivo method or in vitro method?

Claim 35 recites the limitation "compound" in claim 34. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zheng (Bioorg. & Med. Chem. Lett., cited on applicants form 1449).

Zheng discloses Yohimbine dimers exhibiting binding selectivities for human alpha-2a versus alpha-2b adrenergic receptors (see table 1 on page 628). Zheng differs from the instant claims in that it does not teach using these compounds for treating alpha-2 receptor mediated conditions or modulating alpha-2a and alpha-2c receptor activity. However, Zheng teaches that availability of subtype-selective alpha-2 receptor antagonists would greatly help to advance our knowledge of functions mediated by these alpha-2 adrenergic receptor subtypes (see first paragraph on page 627). Therefore, one skilled in the art would have been motivated to use the instant compounds to treat conditions mediated by alpha-2a receptors or to modulate alpha-2a receptors. Furthermore, it would be inherent to modulate alpha-2c receptor subtype also following in vivo administration of these compounds.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charanjit S. Aulakh whose telephone number is (571)272-0678. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

C. S. Aulakh

Charanjit S. Aulakh
Primary Examiner
Art Unit 1625